**TRANSPORT OF DRUGS**

**OBJECTIVES**

1. **Define what is meant by drug absorption** 
   1. The process by which the drug gets from the site of administration into the blood stream
      1. For IV drugs, absorption is bypassed
   2. Major sites of Absorption
      1. GI tract
      2. Lungs
      3. Skin—barrier to absorption
      4. Injection site
2. **Define what is meant by drug distribution** 
   1. Process by which the drug moves from the blood to various tissues and organs of the body
      1. Rate depends on
         1. Permeability of capillaries to the drug
         2. Rate of blood flow to the tissue
         3. Rate of distribution therefore differs for different organs
3. **Describe the properties of a site, which promote drug absorption.** 
   1. Rate of absorption depends on
      1. Area of surface exposed to the drug
         1. ↑ SA= ↑ absorption
      2. Thickness of the barrier
         1. Thin barrier = easier to absorb
      3. How well the site is perused with blood
         1. More blood = more direct contact with the site to absorb into
4. **Identify major site and mechanism of drug absorption following oral administration** 
   1. GI Tract is the major site of drug absorption following oral administration
      1. Mechanism
         1. GI tract has transport systems to absorb items that the body need
            1. this excludes most drugs
         2. Most drugs must be absorbed via **passive non-ionic diffusion** through epithelial cell membranes
            1. Neutral drugs will be absorbed at a rate dependent on their partition coefficient (PC)
            2. Weak acids and bases are absorbed at rates dependent on their PC, their pK and the pH GI tract
            3. Drugs with fixed charges will be very poorly absorbed
         3. ***Note however***: Absorption from the GI tract is made more complex by the existence  of drug transporters and drug metabolizing enzymes in the epithelial cells
         4. **STOMACH** 
            1. Due to acid pH…

Weak bases are **not** be absorbed from the stomach because conc. of uncharged base will be very low

Weak acids can be absorbed from stomach

* + - 1. **SMALL INTESTINE** 
         1. Due to its very large surface area, the SI is the major site of absorption for almost all drugs administered orally

1. **Describe function of GI tract and liver in protecting body against potentially toxic substances** 
   1. **Metabolism by GI tract and liver** 
      1. Transporters, e.g. P-gp can transport some drugs from epithelial cells  back into the gut lumen or the drug may be metabolized in gut
      2. Also, drugs absorbed from the GI tract pass to the liver via the hepatic portal vein before entering the systemic circulation
2. **Recognize that drugs passively absorbed by epithelial cells in the gut can be transported back to the lumen.** 
   1. Transporters, e.g. P-gp can transport some drugs from epithelial cells  back into the gut lumen or the drug may be metabolized in gut
3. **Explain the term “First Pass Effect”** 
   1. **FIRST-PASS EFFECT** 
      1. The fraction of an orally administered drug that is metabolized by the liver and GI tract before reaching the systemic circulation
      2. Some drugs have such a high “first-pass” effect that they are not usually administered orally
         1. **Nitroglycerin**
         2. **Morphine**
         3. **Lidocaine**
         4. **Estradiol**
4. **Explain what is meant by the bioavailability of a drug. Is it the same for a given drug regardless of the route of administration? Is a drug with zero bioavailability useless?** 
   1. ***BIOAVAILABILITY***
      1. The fraction of unchanged drug that reaches the systemic circulation
      2. Why may bioavailability be < 100%?
         1. Absorption < 100%
         2. GI tract metabolism - especially CYP 3A4 and P-gp
         3. Liver may metabolize the drug before it can enter systemic circulation
      3. *NOTE:* A drug with 0% oral bioavailability may still be useful, if the metabolite is the active agent
      4. *IMPORTANT source of drug interactions:* The bioavailability and consequently the plasma concentration of a drug that normally has a low bioavailability due to metabolism can significantly increase if the drug metabolizing enzymes are blocked by another drug.
5. **Describe factors that might decrease bioavailability** 
   1. Absorption <100%
   2. GI tract metabolism—especially CYP3A4 and P-gp
   3. Liver may metabolize the drug before it can enter systemic circulation
   4. \*\*a drug with 0% oral bioavailability may still be useful, if the metabolite is the active agent
   5. \*\*to compensate for low bioavailability due to metabolism you can significantly increase if the drug metabolizing enzymes are blocked by another drug
6. **Explain why sublingual and rectal administration avoids first pass metabolism** 
   1. Because these are directly absorbed into the systemic circulation if they have a favorable enough partition coefficient
      1. Drugs administered rectally have various unpredictable effects and about 50% of the drug goes into systemic circulation while the other goes into hepatic
7. **Explain how IM and SC administration allows control over absorption rates and describe how the drug gets into the circulation** 
   1. IV has the best control over blood concentration
   2. IM and SC allows control over absorption because depending on the solubility (aqueous vs. salt form vs. oil based) you can control how quickly it is taken up into the blood stream.
      1. More soluble = more rapid absorption
   3. Absorption also depends on the blood flow in each of these so things that can effect blood flow (activity, heat, inflammation, etc) can increase drug absorption
8. **Describe topical absorption of drugs and use in providing local and systemic effects** 
   1. Skin is a very good barrier to keep things on the outside from getting into the inside
   2. If the topical has a poor PC it will induce a local effect and not be able to cross the epidermal barrier into the systemic circulation
   3. Now there are more and more drugs that are potent enough with a favorable PC that can be absorbed through the epidermal barrier and into the circulation
      1. These are applied as patches to the skin
         1. Nicotine patch, Nitroglycerin, Scopolamin, Estradiol, Testosterone, Fentanyl
9. **Describe role of blood flow rate in determining rates of distribution** 
   1. More blood flow= better distribution
      1. Distribution is also dependent on the permeability of the capillaries to the drug
   2. The organ with the most blood flow are
      1. Heart
      2. Liver
      3. Kidney
      4. Brain
         1. The brain doesn't have pores in its capillaries so the drug has to have a good PC to get in
   3. The organs that are less perfused are
      1. Muscle
      2. Skin
      3. Viscera
      4. Fat
10. **Describe the barriers to drug distribution that exist within the capillaries, brain, liver, lungs, prostate, joint, placenta** 
    1. **Capillaries**
       1. The pores on the capillaries must allow for drug to be permeable or the drug cannot cross
    2. **Brain**
       1. The brain doesn't have pores in its capillaries but it has tight junction between cells which restricts the paracellular flow of drugs.
       2. Capillaries in the brain are surrounded by glial cells rather than ECF
       3. Capillary endothelial cells contain drug transporters (P-glycoprotien that may pump drugs out of the cell into the blood)
       4. Normally drugs can only enter CNS by passive non-ionic diffusion across cells (4 lipid bilayers must be crossed)---drug needs a favorable PC
          1. A favorable PC doesn't guarantee passage across BBB b/c transporters (P-pg) may transport them back into the blood
          2. Inflammation can increase capillary permeability so when the brain is inflamed (meningitis) pores can open up between cells allowing penicillin entry
       5. Certain areas of the brain lack the barrier---chemoreceptor trigger zone and hypothalamus
    3. **Liver**
       1. Metabolizes drugs that go through and can decrease the distribution
       2. Also liver synthesizes most of the plasma proteins that drugs can bind to and can store on which can decrease or increase the distribution to come tissues
    4. **Lungs**
       1. Have large capillary surface area so good site for drug metabolism/filter
          1. Inactivates many prostaglandins that pass through it
       2. Blood from all organs passes through lungs before being distributed to the rest of the body
    5. **Prostate**
       1. Sertoli cells here are connect by tight junction and do NOT have pores
          1. This limits distribution to sperm and secreted fluid
             1. You don't random substances to get near germ cells because they can cause mutations that can be passed onto offspring
    6. **Joint**
       1. There are NO pores unless joint is inflamed
    7. **Placenta**
       1. Pores are ABSENT
       2. Drugs that are LIPOPHILIC (favorable PC) enter fetal circulation most readily by simple passive diffusion
       3. Only those that are large and have multiple charges and extremely low lipid solubility fail to cross the placenta
       4. ALSO they have P-gp transporters that export drugs and fetal blood is more acidic than the mother so there is potential for ion trapping of weak bases in blood of the fetus
       5. \*\*best to assume that the fetus is to at least some extent exposed to essentially all drugs taken by the mother
11. **Recognize that transporters form an important component of several “barriers” in the body, including the blood brain barrier, the blood CSF barrier, and the placental barrier protecting critical tissues from xenobiotics/drugs.** 
    1. Read # 14 above for BBB and placental barrier
    2. BCSFB
       1. Choroid plexus is found in the lateral 3rd and 4th ventricles and secretes CSF
       2. Cells of the choroid plexus are connected by tight junctions forming the BCSFB
       3. Drugs can only enter CSF and hence the ECF of the brain by passive diffusion across these epithelial cells
       4. The area of the blood-CSF barrier is 1/1000 of the BBB
       5. The choroid plexus also has active transporters that can pump drugs out of the CSF and contains drug metabolizing enzymes
12. **Explain the concept of volume of distribution.** 
    1. Defined as the apparent volume that a drug occupies after absorption and distribution are complete
    2. From the equation: X in blood = (X added/(V blood + V ECF + V ICF)) it is evident that the volume of distribution (Vd) can be calculated from the total amount of drug administered and the concentration of the drug in the blood which can be measured
    3. It is only a true “volume” if the “concentration” of the drug is the same in all compartments/tissues. Drug binding and accumulation of drugs in fat of adipose tissue can inflate the value above the real volume and may be greater than the body’s volume.
13. **Describe the role plasma proteins play in binding certain drugs and how they provide a drug reservoir** 
    1. Most drugs must be carried by the blood and be soluble in water to reach their site of action
    2. Drugs are transported around the body in the blood via the vascular system
    3. Protein binding can provide “store” of drugs and transport drugs in blood
       1. Many drugs are transported in the blood bound to albumin (acidic drugs) or α-1 acid glycoprotein (basic drugs)
    4. Only free drug can cross membranes, bind to receptors and metabolizing enzymes and is filtered by the kidney
       1. 99% of warfarin is bound to plasma proteins
14. **Explain how drugs can compete for binding to plasma proteins and what effect this has on the free concentration and total amount of drug in the blood.** 
    1. When only one drug is administered it can bind to plasma proteins and be in equilibrium with its free concentration of drug
    2. When you add a competing drug then you get a transient increase in free concentration of the drug because it is now competing for binding sites on the plasma protein
       1. It is only transient because increasing the free concentration also increases the elimination of the drug and it will eventually return to its new steady state accounting for the new drug
          1. New steady state has same free concentration of drug but now the total blood concentration is lower (less is now bound to plasma protein) and this can effect drug therapies that monitor total concentration in the blood vs. free and can mislead them into increasing the dose
15. **Recognize diseases can alter levels of plasma proteins.** 
    1. Some diseases can ↓ levels of plasma proteins
       1. Liver diseases (less plasma proteins synthesized)🡪 so less drug binding
       2. Renal disease (nephrotic syndrome)🡪 lead to proteinuria and loss of plasma proteins
       3. \*\*NET—less drug will be bound and there will be an ↑ in free drug concentration relative to total amount of drug in the blood
    2. Some diseases can ↑ evels of plasma proteins
       1. Diseases that induce acute phase responses stimulate protein synthesis
          1. Cancer
          2. Arthritis
          3. Chrohn’s
          4. MI
          5. \*\*release TNFα which stimulates protein synthesis
       2. \*\*NET—more drug will be bound and there will be a ↓ in free dug concentration relative to total drug